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Work Stress and Metabolic and Hemostatic Risk Factors

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Objective: A high level of work stress has been associated with cardiovascular disease. However, the pathophysiological mechanisms underlying this association remain unclear. This study examined the effect of work stress on a cluster of metabolic and hemostatic risk factors. **Methods:** Blood was collected three times, on the first, third, and fifth day of a work week, from 124 middle-aged, white-collar workers. Metabolic measures were insulin, glucose, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and total cholesterol. Hemostatic measures were fibrinogen, tissue-type plasminogen activator activity, tissue-type plasminogen activator antigen, and type 1 plasminogen activator inhibitor antigen. Chronic work stress was defined according to Siegrist's model as 1) a combination of high effort and low reward at work (effort-reward imbalance) or 2) high overcommitment (an exhaustive work-related coping style). **Results:** Overcommitment, but not imbalance or the imbalance-overcommitment interaction, was associated with an impaired fibrinolytic system, as reflected in decreased tissue-type plasminogen activator activity levels and increased type 1 plasminogen activator inhibitor antigen levels on all three measurement occasions. After controlling for body mass index, total cholesterol, triglycerides, high-density lipoprotein/low-density lipoprotein cholesterol ratio, glucose, and insulin, the relation between overcommitment and the fibrinolytic factors was attenuated but remained significant. **Conclusions:** The results suggest that individuals with an exhaustive coping style at work have an impaired fibrinolytic capacity that is possibly due to the effects of chronic stress on insulin resistance. **Key words:** fibrinolysis, insulin resistance syndrome, chronic stress, overcommitment.

BMI = body mass index; HDL = high-density lipoprotein; IRS = insulin resistance syndrome; LDL = low-density lipoprotein; PAI-1 = type 1 plasminogen activator inhibitor; TC = total cholesterol; TG = triglyceride; tPA = tissue-type plasminogen activator.

INTRODUCTION

Recent prospective studies (1, 2) have shown that the risk of coronary disease is associated with various indices of work stress (eg, high job demands, low resources, low income, and low status control). Despite this epidemiological evidence, definite knowledge about the pathophysiological link between work stress and heart disease is still lacking, although several mechanisms have been proposed (3, 4). Experimental animal models and human studies have shown that indices of psychosocial stress are associated with glucose intolerance, hyperinsulinemia, dyslipidemia, and hypertension (5–9). These associations are thought to derive from the hormonal and cardiovascular responses to repeated activation of the autonomic nervous system (9). Although these metabolic factors independently increase the risk for cardiovascular disease, they tend to cluster in certain individuals.

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This aggregation of metabolic risk factors, first described by Reaven (10), is called the insulin resistance syndrome, or IRS, because resistance to insulin-stimulated glucose uptake has been postulated to be the primary defect (11, 12).

Apart from metabolic risk factors, the risk of developing atherosclerosis or atherothrombosis is influenced by the balance between coagulation and fibrinolysis (12, 13). Elevated levels of plasma fibrinogen predict cardiovascular disease (14, 15). tPA activity converts plasminogen into active plasmin, which breaks down intravascular fibrin clots. PAI-1 regulates the concentration of tPA activity by continuously forming inactive tPA–PAI-1 complexes in a well-characterized bimolecular reaction (16). The active part of tPA and PAI-1 (activity) can be measured, as can total levels of tPA and PAI-1 (antigen) that include PAI-1 and tPA in their complexed form (16). tPA antigen seems to be positively associated with risk of myocardial infarction (17, 18). Although less consistently, increased PAI-1 and low tPA activity have also been associated with an increased risk of myocardial infarction (15, 18–20) as well as thrombosis (13, 21). Many studies have demonstrated that an imbalance in coagulation and fibrinolysis is associated with insulin resistance (22, 23). Insulin may exert a direct action on the synthesis of PAI-1 by endothelial cells or hepatocytes or indirectly by plasma TG levels (24, 25) or nonesterified fatty acids (26). Therefore, deficient fibrinolysis is now regarded to be part of IRS (22, 23). Like the metabolic aspects of IRS, fibrinogen, tPA, and PAI-1 are influenced by acute psychological stress (27–29).

Specific studies on the effects of chronic work stress on the variables of IRS are few and inconsistent.

Schnall et al. (30), in a review of the literature, found little evidence for effects of job strain on the lipid profile. In a recent study, however, low decision latitude at work was found to be associated with low HDL cholesterol levels (31). Markowe et al. (32) and Siegrist et al. (33) found a positive association between job stress scores and fibrinogen concentration, but two recent studies failed to replicate this effect (34, 35). Ishizaki et al. (36) showed that high job demands were related to decreased tPA activity, independently of the traditional risk factors. Two further studies reported an association between vital exhaustion, a mood state hypothesized to derive from the reaction to chronic work stress (37), and impaired fibrinolysis (38, 39). Most of the previous studies used heterogeneous populations, which makes it difficult to separate effects of socioeconomic status differences from those of work stress. Also, these studies assessed the effects of work stress on subsets of the metabolic and hemostatic IRS parameters rather than on the full cluster.

The study described here examined whether chronic work stress is associated with fibrinogen and the full cluster of metabolic and fibrinolytic factors of IRS in a group of middle aged, male, white-collar workers. Chronic work stress was assessed by a questionnaire based on Siegrist's effort-reward imbalance model (40). This model has been shown to predict cardiovascular disease or shifts in cardiovascular disease risk parameters in several studies (1, 34, 40, 41). The model defines chronically stressful experience at work in terms of a mismatch between high effort spent and low reward received in occupational life. Two sources of effort at work are explicitly distinguished: an extrinsic source, the demands on the job (situational), and an intrinsic source, a personal pattern of coping with work demands (personal). The model of effort-reward imbalance states that lack of reciprocity between costs and gains defines a state of emotional distress with special propensity to autonomic arousal and neuroendocrine stress responses, resulting in higher cardiovascular risk (42). This lack of reciprocity, or mismatch, is expressed by two summary measures of work stress: 1) by calculating the ratio between extrinsic effort and rewards (imbalance) and 2) by the sum score of the intrinsic effort component (overcommitment). This last component is by itself a mismatch score because those individuals who score high are characterized by excessive overcommitment. They tend to spend an inadequate amount of effort that is not met by the externally defined rewards.

Several studies have shown intraweek mood changes and fluctuations in daily stress during the work week (43–46), with negative mood and stress usually lower in the weekend compared with the work week. There is

abundant evidence of effects of daily mood and stress on catecholamines (45) and cortisol (46), which are both important determinants of many of the risk parameters assessed in our study (6, 27, 28, 47–49). There are currently no studies directly addressing intraweek changes in hemostatic or metabolic blood variables. It is also unknown whether such short-term fluctuations are influenced by the level of overcommitment or effort-reward imbalance. Apart from assessing the main effects of effort-reward imbalance and overcommitment on metabolic and hemostatic risk factors, our study explored the effects of imbalance and overcommitment on the changes in these variables in the course of a single work week.

MATERIALS AND METHODS

Subjects

The study population consisted of middle-aged (range, 35–55 years; mean \pm SD, 45.2 ± 5.3 years), white-collar workers, all working at the same large computer company. All subjects, who worked in departments where mainly sitting work was done, were considered eligible if they were between 35 and 55 years of age. Eight hundred twenty subjects received the effort-reward imbalance work stress questionnaire (see below). Four hundred sixty subjects (57%) returned the questionnaire, and from this group, 300 were willing to participate in the study. Of these 300 subjects, 148 subjects (126 men, 22 women), working in departments where subjects showed a large variation in work stress scores, were selected for blood sampling. The mean overcommitment score for the selected group was 11.0 ± 4.2 , which was not significantly different from that of the nonselected group (11.2 ± 4.7). Also, the percentage of subjects with imbalance between effort and reward was not significantly different between the selected and nonselected groups (20.9% and 18.6%, respectively). The analyses in this study were restricted to men because the number of women in the selected group, as a consequence of the male-female distribution in the company, was too small for the planned statistical analyses.

Of the 126 men, two subjects were excluded because of a glucose value >7.8 mmol/liter, which is an indicator of diabetes mellitus according to World Health Organization criteria. None of the subjects received treatment for hypertension, hyperlipidemia, or diabetes mellitus, and all subjects were free of overt cardiovascular disease. The study protocol was approved by the ethics committee of Vrije Universiteit, and all subjects gave written consent before entrance into the study.

Measures

Work Stress. A Dutch version of the effort-reward imbalance questionnaire developed by Siegrist was used to measure perceived chronic work stress. The underlying model defines chronically stressful experience at work in terms of mismatch between high effort spent and low reward received in occupational life. The model defines two sources of high effort at work: 1) the demands of the job (extrinsic effort) and 2) the motivation and ability of the individual worker to cope with a demanding situation (intrinsic effort). Extrinsic effort is measured by six items, and occupational reward is measured by 12 items that refer to esteem reward, monetary gratification, and status control. Intrinsic effort was assessed by 29 items

that refer to four factors: 1) need for approval, 2) competitiveness, 3) impatience and a disproportionate level of irritability, and 4) inability to withdraw from work obligations. The total sum of the four subscales defines the sum score of intrinsic effort, which is also called overcommitment.

The analysis was based on two summary measures, imbalance and overcommitment. Imbalance is the ratio between extrinsic effort and reward multiplied by 2. An imbalance >1 means high chronic work stress, and an imbalance ≤ 1 means low chronic work stress (4). Overcommitment is the sum score of intrinsic effort. A value in the upper tertile (high overcommitment) indicates a critically high level associated with adverse health effects (50, 51). The lower two tertiles comprised the low overcommitment group. Reliabilities (Cronbach's α) for the overcommitment score as well as for the scores for the reward and extrinsic effort subscales were 0.79, 0.75, and 0.66, respectively. Subjects were classified on the basis of scores for imbalance and overcommitment into high and low groups.

Blood Variables. Blood was collected by venipuncture and sampled in six different tubes in the following order: serum (3 ml), serum with cloth activator (5 ml), stabilyte (5 ml), citrate (5 ml), ethylenediaminetetraacetic acid (3 ml), and NaF (2 ml). All tubes were centrifuged at 2000g for 20 minutes at 4°C. For determination of TC, TGs, and HDL, the tube containing serum with cloth activator was used. Lipid determinations were performed on the same day using the Vitros 250 clinical chemistry analyzer (Johnson & Johnson, Rochester, NY) with Vitros clinical chemistry slides for TC and TGs. HDL was measured after a precipitation step with HDL cholesterol precipitant (Boehringer Mannheim, Mannheim, Germany). LDL was calculated using the formula of Friedewald (52). Fasting insulin was measured with an immunoradiometric assay kit (Medgenix Diagnostics, Fleurus, Belgium) by means of the serum tube. Aliquots of serum were stored at -20°C , and all samples were analyzed simultaneously; no sample was stored for >5 months.

Fasting glucose was measured in plasma (NaF tube). Aliquots of plasma were stored at -20°C , and the glucose concentration was determined within 5 days using the Hitachi 747 automatic analyzer by the hexokinase method (Hitachi, Ltd., Tokyo, Japan).

Blood collection and handling of the hemostatic variables were performed according to the European Concerted Action on Thrombosis assay procedure (53). Stabilyte blood was collected for the determination of tPA activity, and citrated blood was collected for the determination of PAI-1 antigen, tPA antigen, and fibrinogen. Immediately after collection, the tubes were placed in melting ice and centrifuged within 60 minutes. Aliquots of plasma were snap-frozen immediately and stored at -80°C . All samples were analyzed simultaneously in a single batch. No sample was stored for >8 months. tPA activity was measured using the biofunctional immunosorbent assay Chromolize tPA (Biopool, Umeå, Sweden). PAI-1 antigen was measured using the Innotest PAI-1 immunoassay (Innogenetics, Zwijndrecht, Belgium) (54). tPA antigen was measured using the enzyme immunoassay Imulyse tPA (Biopool, Umeå, Sweden). No effort was made to separately assess PAI-1 activity because it has been reported to correlate very highly with PAI-antigen (16). Fibrinogen was measured using the STA coagulation analyzer (STAG-O, Asnières, France) and the STA fibrinogen kit (Boehringer Mannheim, Mannheim, Germany). The intraassay and interassay coefficients of variation were $<5.0\%$ and $<7.0\%$ for fasting insulin, $<4.0\%$ and $<6.0\%$ for TC, $<3.5\%$ and $<5.0\%$ for HDL, $<3.0\%$ and $<5.0\%$ for TGs, $<7.5\%$ and $<10\%$ for tPA activity, $<10\%$ and $<10\%$ for PAI-1, $<10\%$ and $<12\%$ for tPA antigen, and $<5\%$ and $<7\%$ for fibrinogen, respectively.

Behavioral Factors. It is well known that age, smoking habits, alcohol consumption, physical activity at leisure, and education level may influence metabolic factors. These confounders were assessed by a questionnaire. Smoking status was measured on a four-

point scale with the following ranking: 1) nonsmoker, 2) former smoker, 3) smoking several times a week, and 4) smoking several times a day. The seven-point scale for measuring educational level ranged from primary school to university level. Physical activity was assessed by asking the following question: "How many times a week do you exercise till sweating in your leisure time?" Answer ranged from 0 (zero times per week) to 4 (four or more times per week). With regard to alcohol consumption, subjects were categorized into four groups: 1) <6 glasses per week, 2) 6 to 10 glasses per week, 3) 11–20 glasses per week, and 4) >20 glasses per week.

Procedure

Blood samples were obtained from each subject at the workplace on Monday, Wednesday, and Friday. This was done between 8:00 and 9:30 AM to control for circadian variations (55). Subjects were asked to fast and to refrain from use of alcohol, coffee, and tea after 11:00 PM the preceding night. All samples were obtained with the subject seated after the subject had rested for at least 15 minutes. Body weight and length were measured without shoes to calculate BMI (in kg/m^2).

Data Analysis

The following variables were log transformed before statistical analysis to make the distributions more symmetrical: insulin, TGs, tPA activity, fibrinogen, and PAI-1. Mean values presented were transformed back into the original scale. Differences between the groups with respect to age, BMI, smoking habits, alcohol consumption, and physical activity were tested by one-way analysis of variance. To test for intraweek effects and differences between the groups, a general linear models procedure was used. TC, LDL/HDL ratio, TGs, insulin, glucose, fibrinogen, tPA antigen, tPA activity, and PAI-1 were analyzed as dependent variables, with day as a within-subject factor and overcommitment and imbalance as between-subject factors. When overall intraweek effects, group effects, or interactions were found, univariate tests were performed to identify the individual variables that were responsible for the effects. p values were adjusted for multiple comparisons with the Holm simultaneous testing procedure as described by Aickin and Gensler (56). Roy-Bargman stepdown F tests were used to evaluate the independent contribution of the metabolic and hemostatic factors to work stress. Statistical tests were performed using SPSS, version 7.5 for Windows, and statistical significance was defined as $p < .05$.

RESULTS

Intraweek Effects

Table 1 shows mean values for the metabolic and hemostatic factors on Monday, Wednesday, and Friday for the total group.

Intraweek (day) effects were analyzed by multivariate analysis (general linear models procedure) with the values on Monday, Wednesday, and Friday as repeated measurements. This analysis showed a significant intraweek effect ($F = 4.457$, $p = .000$). Univariate analyses showed that glucose and TC were responsible for this effect. Glucose levels were significantly higher on Monday than on Wednesday and Friday ($F = 22.64$, $p = .000$). For TC, a significantly higher value was

WORK STRESS AND METABOLIC AND HEMOSTATIC RISK FACTORS

TABLE 1. Mean and ($N = 124$) of Metabolic and Hemostatic Risk Factors on Monday, Wednesday, and Friday

Variable	Monday	Wednesday	Friday	p
TC (mmol/liter)	5.47 \pm 0.96	5.59 \pm 1.00	5.46 \pm 1.00	.000 ^a
TGs (mmol/liter) ^b	1.43 (0.42–7.34)	1.57 (0.55–8.11)	1.51 (0.51–8.62)	.015
HDL/LDL ratio	3.31 \pm 1.36	3.39 \pm 1.31	3.37 \pm 1.33	.518
Glucose (mmol/liter)	5.89 \pm 0.55	5.69 \pm 0.47	5.71 \pm 0.47	.000 ^a
Insulin (mU/liter) ^b	6.60 (2.36–31.83)	6.49 (2.78–22.80)	6.63 (1.67–26.55)	.581
PAI-1 (ng/ml) ^b	72.5 (11.0–287.3)	65.8 (10.4–280.5)	66.6 (10.0–272.5)	.145
tPA activity (IU/ml) ^b	0.54 (0.03–2.34)	0.54 (0.05–2.68)	0.52 (0.07–1.61)	.574
tPA antigen (ng/ml)	10.25 \pm 3.64	10.17 \pm 3.66	10.07 \pm 3.57	.713
Fibrinogen (g/liter) ^b	2.93 (1.97–5.32)	2.93 (1.71–4.71)	2.93 (1.82–4.58)	.861

^a Significant intraweek effect (after correction for multiple testing according to Holm's procedure).

^b Back-transformed logarithmic mean and range.

found on Wednesday than on Monday and Friday ($F = 9.62$, $p = .000$). The other variables showed no intraweek effect (Table 1). Overall, the retest correlations (reliability) for Monday-Wednesday, Wednesday-Friday, and Monday-Friday were all highly significant and ranged from 0.67 for tPA activity to 0.95 for LDL/HDL ratio.

Interrelationship of the Blood Parameters

Significant intercorrelations between the metabolic and hemostatic risk factors are shown in Table 2. These correlations were computed on the mean values of all variables across Monday, Wednesday, and Friday.

The parameters considered to be part of IRS showed a systematic pattern of intercorrelations (Table 2, *lower left triangle*). Fibrinogen, usually not considered to be part of IRS, was not systematically related to the parameters of IRS. The correlation of insulin with the fibrinolytic variables was higher than with the metabolic variables. BMI was correlated with all variables except TC and fibrinogen. This testifies to the central

role of BMI in IRS. When BMI was partialled out, all correlations decreased, but most remained significant (Table 2, *upper right triangle*). Age was not related to any of the variables.

Chronic Work Stress Effects

To test the effects of chronic work stress, subjects were divided into groups on the basis of their scores for imbalance and overcommitment. Twenty-eight subjects (23%) experienced a mismatch between high effort and low reward at the workplace (imbalance > 1). The other 96 subjects were classified as low imbalance. Subjects in the upper tertile of overcommitment were considered high in overcommitment, and the other two tertiles were low in overcommitment. As shown in Table 3, 15 subjects (12.4%) reported high overcommitment and high imbalance, the group with the most stressful experiences at work. Table 3 also shows the personal characteristics and the IRS variables as a function of high and low overcommitment and imbalance. There were no interactions or main effects of imbalance and overcommitment on the con-

TABLE 2. Pearson Correlation Coefficients Between Metabolic and Hemostatic Factors (Mean Values of Monday, Wednesday, and Friday) and BMI ($N = 124$)^a

	TC	TGs	HDL/LDL Ratio	Glucose	Insulin	PAI-1	tPA activity	tPA antigen	Fibrinogen	BMI
TC	—	0.51	0.45						0.25	—
TGs	0.48	—		0.49		0.45	−0.27	0.37		—
HDL/LDL ratio	0.44	0.54	—			0.24		0.29		—
Glucose		0.24	0.24	—	0.28					—
Insulin		0.32	0.31	0.45	—	0.37	−0.34	0.35		—
PAI-1		0.55	0.36	0.38	0.59	—	−0.66	0.60		—
tPA activity		−0.41	−0.33	−0.34	−0.56	−0.79	—			—
tPA antigen		0.46	0.37	0.35	0.50	0.69	−0.40	—		—
Fibrinogen	0.25		0.23						—	—
BMI		0.35	0.29	0.44	0.57	0.61	−0.59	0.42		—

^a Only correlations at a significance level of $p < .01$ are presented. Upper triangle: Partial correlation coefficients with BMI partialled out. Lower triangle: unadjusted correlation coefficients.

TABLE 3. Work Stress, Personal Characteristics, and Metabolic and Hemostatic Factors (Mean Values of the Three Measurement Days) As a Function of Imbalance Nested Under Overcommitment

	Low Overcommitment		High Overcommitment		Total (N = 124)
	Low Imbalance (N = 71)	High Imbalance (N = 13)	Low Imbalance (N = 25)	High Imbalance (N = 15)	
Imbalance	0.63 ± 0.14	1.19 ± 0.19	0.72 ± 0.13	1.24 ± 0.27	0.78 ± 0.29
Overcommitment	8.54 ± 2.64	9.54 ± 2.67	16.48 ± 3.55	17.33 ± 4.05	11.35 ± 4.87
Age (years)	45.5 ± 5.6	46.0 ± 6.0	44.4 ± 5.1	44.5 ± 4.0	45.23 ± 5.3
BMI (kg/m ²)	24.8 ± 2.7	24.8 ± 2.2	25.6 ± 3.2	25.9 ± 2.7	25.1 ± 2.8
Alcohol use ^a	2.0 ± 1.0	1.8 ± 1.1	2.2 ± 1.3	2.0 ± 0.9	1.98 ± 1.02
Current smokers (%)	25.4	38.5	40.0	26.7	29.6
Education ^a	5.0 ± 1.4	4.9 ± 1.9	4.8 ± 1.9	5.2 ± 1.5	5.0 ± 1.4
Physical activity ^a	1.5 ± 1.1	1.5 ± 1.1	1.4 ± 1.3	1.3 ± 1.0	1.46 ± 1.12
Years of service (years)	22.1 ± 7.2	21.8 ± 5.3	21.3 ± 6.9	18.5 ± 7.8	21.47 ± 7.0
TC (mmol/liter)	5.50 ± 0.95	5.47 ± 1.20	5.42 ± 0.90	5.81 ± 1.02	5.52 ± 0.97
TGs (mmol/liter) ^b	1.42 (0.62–8.13)	1.61 (0.63–5.05)	1.67 (0.55–4.10)	1.55 (0.65–3.97)	1.50 (0.55–8.13)
HDL/LDL ratio	3.23 ± 1.19	3.35 ± 1.30	3.62 ± 1.43	3.85 ± 1.83	3.40 ± 1.35
Glucose (mmol/liter)	5.71 ± 0.46	5.62 ± 0.35	5.87 ± 0.50	5.91 ± 0.44	5.76 ± 0.46
Insulin (mU/liter) ^b	6.21 (3.01–20.71)	6.44 (3.34–22.24)	7.60 (2.55–23.58)	6.92 (3.34–13.48)	6.57 (2.55–23.58)
PAI-1 (ng/ml) ^b	60.3 (10.5–247.9)	59.05 (15.7–120.9)	89.1 (30.3–190.7)	90.4 (27.9–273.3) ^c	68.2 (10.5–273.3)
tPA activity (IU/ml) ^b	0.59 (0.16–1.46)	0.61 (0.33–1.30)	0.47 (0.14–1.72)	0.37 (0.06–0.76) ^c	0.53 (0.06–1.72)
tPA antigen (ng/ml)	9.90 ± 3.44	10.38 ± 4.06	10.54 ± 2.92	10.42 ± 3.11	10.15 ± 3.35
Fibrinogen (g/liter) ^b	2.96 (2.11–4.60)	2.94 (2.34–3.62)	2.97 (2.31–3.58)	2.75 (1.88–3.91)	2.93 (1.88–4.60)

^a See Materials and Methods for explanation.^b Back-transformed logarithmic mean and range.^c Significantly different between high and low overcommitment groups (after correction for multiple testing according to Holm's procedure).

founding variables (ie, age, smoking habits, alcohol consumption, physical activity at leisure, education level, and years working at the company). Most notably, BMI did not differ between groups.

Multivariate analysis on the metabolic and hemostatic factors revealed no significant differences between the high and low imbalance groups. Also, imbalance and overcommitment showed no interaction. Thus, simultaneous manifestation of high imbalance and high overcommitment did not show a cumulative effect on the blood variables. Also, no interactions between work stress measures and day of the week were found. There was, however, a main effect of overcommitment ($F = 2.47$, $p = .013$). This multivariate effect, present on all 3 days, is portrayed in Figure 1, which shows the sum of nine standardized risk variables on Monday, Wednesday, and Friday. All nine parameters were first standardized using a normalized Z score. The summed risk score was computed as the sum of these nine Z scores using the following formula: $Z_{\text{glucose}} + Z_{\text{insulin}} + Z_{\text{TC}} + Z_{\text{TG}} + Z_{\text{fibrinogen}} + Z_{\text{PAI-1}} + Z_{\text{tPA antigen}} - Z_{\text{tPA activity}} - Z_{\text{HDL}}$. Clearly, overcommitment by itself and not necessarily in combination with imbalance had an effect on the risk profile.

For optimal analysis of the overcommitment effects, the general linear model was simplified by eliminating

imbalance as a between-subject factor. Univariate analyses showed higher levels of PAI-1 ($F = 12.23$, $p = .001$), insulin ($F = 4.61$, $p = .034$), and glucose ($F = 3.93$, $p = .050$) and lower levels of tPA activity ($F = 16.57$, $p = .000$) in the high overcommitment group. After Holm's correction for simultaneous testing, only tPA activity and PAI-1 remained different between the two groups. When the analysis was performed with BMI in the model as a covariate, overcommitment was still associated with tPA activity and PAI-1 ($F = 15.94$, $p = .000$ and $F = 10.852$, $p = .001$, respectively).

The results of the univariate analyses showed that PAI-1 and tPA activity are significantly associated with overcommitment. To evaluate whether tPA activity and PAI-1 are associated with overcommitment independently of the metabolic risk factors, models with TC, TGs, HDL/LDL ratio, glucose, and insulin as covariates were fitted (Roy-Bargman stepdown F tests). Both tPA activity and PAI-1 still predicted overcommitment after this procedure ($F = 9.07$, $p = .003$ and $F = 9.81$, $p = .002$ respectively). However, the correlation between PAI-1 and tPA activity was very high (-0.79). Addition of either tPA activity or PAI-1 as a further covariate rendered the association with overcommitment nonsignificant ($F = 1.92$, $p = .17$). Thus, PAI-1 and tPA activity are both associated with overcommitment, but not independently.

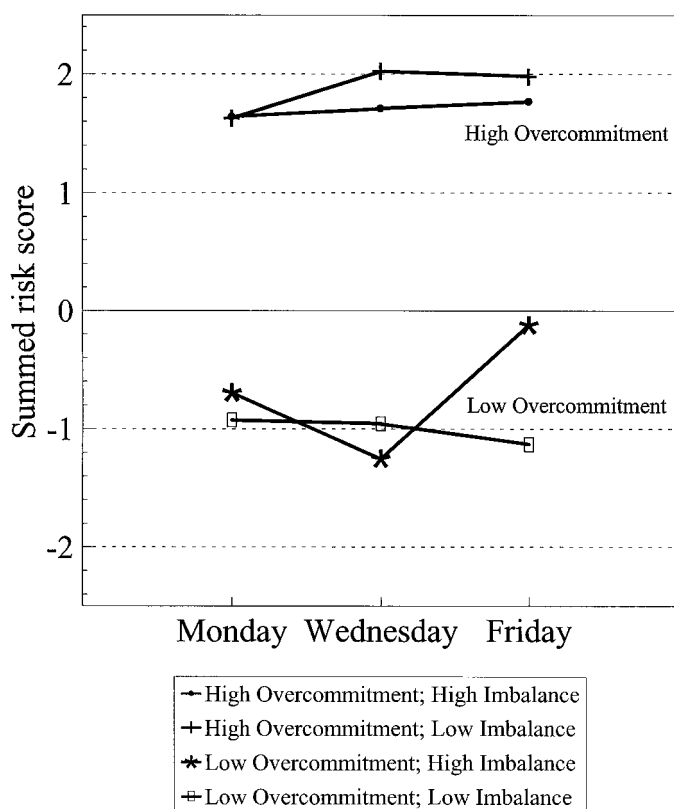


Fig. 1. All nine parameters as a function of effort-reward imbalance and overcommitment. The risk scores were first standardized using normalized Z scores. The summed risk score was computed as the sum of these nine Z scores using the following formula: $Z_{\text{glucose}} + Z_{\text{insulin}} + Z_{\text{TC}} + Z_{\text{TG}} + Z_{\text{fibrinogen}} + Z_{\text{PAI-1}} + Z_{\text{tPA antigen}} - Z_{\text{tPA activity}} - Z_{\text{HDL}}$.

DISCUSSION

The aim of the study described here was to determine the effects of work stress on a cluster of metabolic and hemostatic risk factors. Previous studies have provided evidence of short-term effects of acute stress on several of these variables (6, 27, 28, 57, 58). However, such small acute effects may be rapidly undone. For instance, changes in tPA activity are almost instantly compensated by circulating PAI-1 to maintain equilibrium (16, 59). Likewise, stress-induced release of free fatty acids may be undone before cholesterol synthesis (6). Only stressors of longer duration are likely to lead to permanent changes in lipid metabolism and fibrinolysis. Chronic work stress was defined in this study by effort-reward imbalance as well as overcommitment, an exhaustive coping style. There is evidence that either imbalance or overcommitment by itself or the specific combination of the two components is associated with an unfavorable cardiovascular risk profile (2, 4, 33, 34). Because imbalance reflects high work demand and because overcommitment might

cause incomplete unwinding after work, high work stress may lead to an accumulation of work-related fatigue toward the end of the work week. We, therefore, also explored an interaction of chronic work stress with day of the week.

No evidence was found in any of the groups for a cumulative work stress effect on any of the blood variables. Only glucose and TC showed a significant intraweek effect, but these effects did not reflect an accumulation of stress. The highest glucose levels were found on Monday, and the highest TC levels were found on Wednesday. This may reflect different eating patterns or alcohol consumption on different weekdays or from work week to weekend. All risk factors assessed in this study are, in fact, influenced by these behavioral factors (12, 57, 60, 61). Thus, it is possible that eating patterns or alcohol consumption somehow masked intraweek changes. With this caveat in mind, our results do not provide evidence for changes in metabolic and hemostatic risk factors as a function of weekday. This was independent of chronic work stress; that is, no differential intraweek effects were found in subjects with high imbalance or overcommitment scores.

We found higher levels of PAI-1 than previous studies that used comparable methods for PAI-1 analyses (19). Because blood for PAI-1 analyses was collected on citrate anticoagulation instead of on stabilyte, accidental leakage of PAI-1 from platelets could have inadvertently raised PAI-1 levels. To test this, β -thromboglobulin, a sensitive indicator of platelet contamination, was measured in 12 samples with the highest PAI-1 levels. The median β -thromboglobulin value was 42 IU/ml (interquartile range, 27–87 IU/ml), which is entirely within acceptable values. Thus, high PAI-1 values were not due to accidental increased leakage of PAI-1 from platelets. We attribute the high PAI-1 values to circadian rhythm effects (55). Blood sampling was always conducted in the morning (between 8:00 and 9:30 AM) and reflects the increase in PAI-1 seen during the latter part of the night. Other studies, like that of Van der Bom et al. (19), sampled throughout the day, which leads to lower values. This suggested effect of time of sampling implies that future studies should pay more attention to possible diurnal characteristics of PAI-1 antigen.

Neither imbalance nor overcommitment was related to fibrinogen level in our subjects, which contrasts with other studies (32, 33). However, a recently published large cross-sectional study among 3427 Swedish men and women also failed to confirm the relation between work stress and fibrinogen (34). Fibrinogen levels were not higher in men who reported a high effort-reward ratio. Also, in a study by Mattiasson and Lindgarde (35), occupational stress did not correlate

with fibrinogen concentration, and men who reported threatened job loss did not have higher fibrinogen concentrations than other men. There is growing evidence for the fact that social status, measured by employment grade, is inversely related to fibrinogen concentration (62, 63). If it is true that low-grade employment is associated with more pronounced job stress, then results from heterogeneous groups are difficult to interpret because job stress in part reflects social class effects. Our study was conducted in a homogeneous group of white-collar workers with low variation in education level, an index of social class, and our results did not show an effect of work stress on fibrinogen levels. Thus, the current evidence suggests that social class, more than work stress, influences fibrinogen levels.

In the study described here, neither imbalance nor imbalance-overcommitment interaction was associated with the IRS risk factors. This contrasts with previous findings of an unfavorable lipid profile in middle-aged men with high imbalance (33) and with results of a study in which workers with high job demands showed low tPA activity (37). Assessment of imbalance in our study was based on a single measurement. It did not take into account the duration of imbalance, effort-reward in previous jobs, or possible effects of periods of unemployment. These factors may complicate the interpretation of our self-reported imbalance measure (64). However, all of our subjects were between 35 and 55 years of age, and the average number of years of service in our study was 21.2 years, meaning that most subjects developed their career at the same computer company and had not been unemployed for several years. Item analyses showed very little variance in two of the three aspects of reward: subjective experience of low status control (including job instability) and low economic reward (income). These aspects, however, largely determine intensity of stressful experience and are the most important variables in predicting cardiovascular disease (1, 4, 47, 64). Thus, in this homogenous white-collar population, effort-reward imbalance depended mainly on low esteem reward, which may explain why it was not associated with risk profile.

In contrast to imbalance, overcommitment showed a significant multivariate association with the metabolic and hemostatic risk profile, as summarized in Figure 1. In particular, overcommitment was associated with an impaired fibrinolytic system, as reflected in lower tPA activity and higher PAI-1. Overcommitment has evolved from a critical analysis of the global pattern of type A behavior and tells something about the individual's way of coping with work demands. Individuals who score high on over-

commitment are competitive, impatient, have a high need for approval, and are unable to "let go." In the long run, they are at risk for feelings of exhaustion and physiological breakdown (50). Overcommitment resembles the behavior style that is described to precede the state of vital exhaustion (65). Vital exhaustion is a mood state that is characterized by excess fatigue, a decrease in energy, and feelings of helplessness or a sense of loss of control (37). Prospective evidence shows it to be an independent predictor of first myocardial infarction (65, 66). Two recent studies showed a relation between vital exhaustion and deficient fibrinolysis. Kop et al. (39) revealed significantly higher PAI-1 activity levels in a well-defined group of exhausted subjects. Räikkönen et al. (38) found that vital exhaustion was related to elevated PAI-1 antigen. Our results are in line with these observations but suggest that fibrinolytic impairment can be found already in the immersive coping phase preceding vital exhaustion.

In previous studies on vital exhaustion, the relation between vital exhaustion and PAI-1 disappeared after correction for obesity, insulin, cholesterol, and TGs (38, 39). Our study confirmed the pattern of significant correlation between BMI and metabolic and fibrinolytic factors. The relationship between overcommitment and fibrinolysis, however, remained intact after correction for BMI, insulin, cholesterol, and TGs. The pattern of correlations between obesity and metabolic risk factors and deficient fibrinolysis has extensively been reported before, and insulin resistance has been assumed to be the underlying factor (11, 23, 25, 67). It is attractive to summarize the currently available studies on overcommitment and the ensuing vital exhaustion by hypothesizing that they affect insulin sensitivity and that this leads to secondary deficits in metabolic and fibrinolytic factors. The exact neuroendocrine basis of this psychosomatic link remains to be elucidated, but current evidence suggests that the pituitary-adrenocortical axis is implicated more than the sympathetic-adrenal axis. The crucial aspect of vital exhaustion and overcommitment is loss of control associated with a submissive, defeated reaction. This type of reaction is characterized mainly by an increase in cortisol secretion together with impaired production of sex steroid hormones (68, 69). In addition, cortisol has been strongly implied in the pathogenesis of insulin resistance, possibly through direct effects on insulin metabolism (48) or indirect effects on central fat distribution (49, 69). Several studies corroborate the idea that psychosocial stress affects insulin resistance through activation of the hypothalamic-pituitary-adrenal axis. Keltikangas-Järvinen et al. (70)

showed that vital exhaustion was correlated with low levels of adrenocorticotrophic hormone and increased levels of cortisol, insulin, and glucose. Nilsson et al. (71) showed that free testosterone levels were decreased in subjects with high psychosocial stress who also had higher plasma insulin levels.

In summary, our study points to impaired fibrinolysis in subjects scoring high on overcommitment. High PAI-1 and low tPA activity, indicators of decreased fibrinolysis, contribute to persistence of fibrin and subsequent thrombus formation. Thus, they present a possible pathway for the often reported link between subjective experience of work stress and atherosclerosis and cardiovascular disease.

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WORK STRESS AND METABOLIC AND HEMOSTATIC RISK FACTORS

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